Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

ASGE American Society for Gastrointestinal Endoscopy

Enhanced EUS imaging (with videos)

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Background and Aims: EUS remains a primary diagnostic tool for the evaluation of pancreaticobiliary disease. Although EUS combined with FNA or biopsy sampling is highly sensitive for the diagnosis of neoplasia within the pancreaticobiliary tract, limitations exist in specific clinical settings such as chronic pancreatitis. Enhanced EUS imaging technologies aim to aid in the detection and diagnosis of lesions that are commonly evaluated with EUS.

Methods: We reviewed technologies and methods for enhanced imaging during EUS and applications of these methods. Available data regarding efficacy, safety, and financial considerations are summarized.

Results: Enhanced EUS imaging methods include elastography and contrast-enhanced EUS (CE-EUS). Both technologies have been best studied in the setting of pancreatic mass lesions. Robust data indicate that neither technology has adequate specificity to serve as a stand-alone test for pancreatic malignancy. However, there may be a role for improving the targeting of sampling and in the evaluation of peritumoral lymph nodes, inflammatory pancreatic masses, and masses with nondiagnostic FNA or fine-needle biopsy sampling. Further, novel applications of these technologies have been reported in the evaluation of liver fibrosis, pancreatic cysts, and angiogenesis within neoplastic lesions.

Conclusions: Elastography and CE-EUS may improve the real-time evaluation of intra- and extraluminal lesions as an adjunct to standard B-mode and Doppler imaging. They are not a replacement for EUS-guided tissue sampling but provide adjunctive diagnostic information in specific clinical situations. The optimal clinical use of these technologies continues to be a focus of ongoing research. (Gastrointest Endosc 2021;93:323-33.)

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an effect on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a Manufacturer and User Facility Device Experience (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology status evaluation reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the Committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database

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was searched through May 2020 for relevant articles by using relevant key words such as "EUS," "endoscopic ultrasound," "elastography," "contrast-enhanced," and "tissue harmonics," among others. Technology status evaluation reports are scientific reviews provided solely for educational and informational purposes. Technology status evaluation reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

EUS has an established role in the evaluation of intraluminal and extraluminal GI pathology. Over successive generations of US processors and echoendoscopes, the spatial resolution of standard B-mode US imaging has improved significantly. The addition of FNA and fine-needle biopsy sampling further expands the diagnostic capability of EUS. However, some limitations remain in differentiating benign from malignant disease. Technical innovations such as contrast-enhanced EUS (CE-EUS), tissue harmonic imaging, and elastography (EG) have sought to address these limitations. Although these techniques have been used routinely for many years during transabdominal US and echocardiography, their adoption during EUS has not been widespread. Data from investigations of these adjunctive modalities have accrued and now allow a better understanding of their performance and utility in various clinical scenarios.

TECHNOLOGY UNDER REVIEW

Elastography

EG is a modality that evaluates tissue stiffness by its response to compression. US waves travel at variable speeds through tissues of different stiffness. Compression of tissue changes its mechanical properties and its reflection of US waves (Fig. 1). Abnormal lesions often deform differently in response to compression compared with surrounding normal tissue. For example, malignant tumors exhibit increased tissue stiffness compared with benign tumors or normal tissue.[1-3] EG compares the spatial arrangement of the tissue and the velocity of US waves at rest and after compression.[4-6]

EG with transcutaneous US has been used in the evaluation of organs such as breast, thyroid, and liver[7] and is also available for use with EUS.[4-6] EG may be used during imaging with standard curved linear array or electronic radial echoendoscopes, provided the processor features an EG mode. This is typically an additional software package that can be purchased (Table 1). During real-time EG, the tissue response to both external mechanical stimuli (eg, pushing the endoscope against the GI wall) and/or physiologic movement (eg, vascular pulsations or respirations) is measured. The stiffness of the tissue is color coded and thus provides a qualitative, real-time assessment of tissue elasticity.

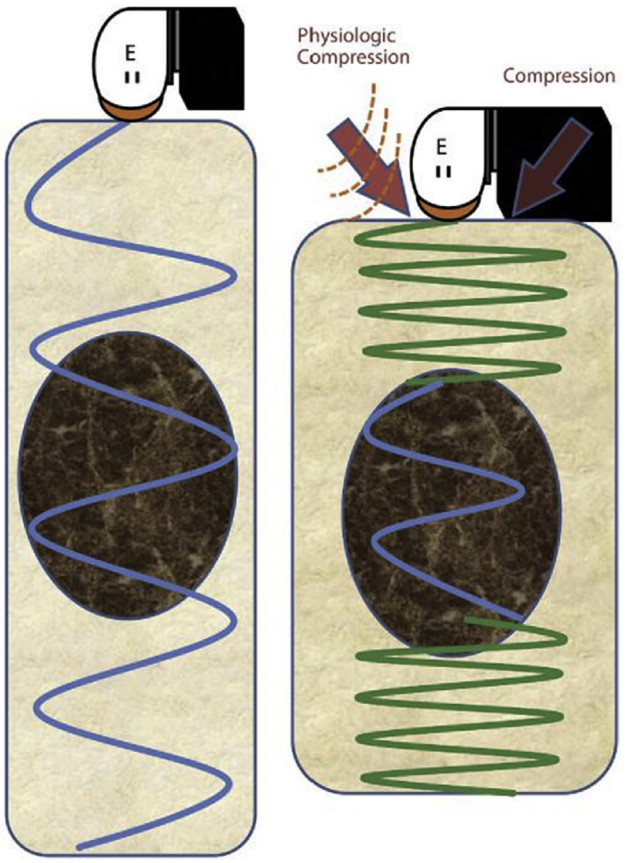

Figure 1. The principle of elastography. The tissue is evaluated with US. At rest, the harder tissue (depicted as the *circular mass*) within the softer organ (*left*). After compression, the harder tissue will be less distorted than the surrounding tissues. The US waves will travel faster through the less-deformed hard mass (*right*). *E,* Echoendoscope.

Measurements of elasticity can be divided into qualitative methods and quantitative methods. The primary qualitative method is an overlay between standard B-mode imaging and an EG color spectrum (Fig. 2). This can also be presented in a split-screen format to aid the endosonographer in identifying areas of increased tissue stiffness (Fig. 3). The qualitative color overlay is frequently heterogeneous because of areas of variable tissue stiffness (Video 1, available online at www.giejournal.org). As such, a subjective quantitative elasticity score (1-5) has been used in some studies with score of 1 being primarily soft tissue (red) and a score of 5 being primarily hard tissue (blue).[8]

Quantitative EG outputs include strain ratio and strain histogram. The strain ratio provides a ratio of stiffness between an area of interest and a reference. The reference area has not been standardized but is usually an adjacent normal area undergoing the same degree of physiologic stress and is ideally a similar distance from the transducer. Some experts advocate that the reference should be a small soft area between the lesion of interest and the gastroduodenal wall (Fig. 4).[9,10] Once an area of interest is selected, the heterogeneous strain pattern may also be

TABLE 1. Available US processors with advanced imaging features

	Olympus EU-ME2 premier plus	Olympus Prosound f75	Pentax Hitachi Preirus	Fujinon SU-1	Hitachi Arietta Olympus
Base price (U.S. dollars)	$182,000	$236,000	$231,750	$155,555	$267,000
Elastography price (U.S. dollars)	Included	$30,000	$25,000	Inc	$30,000
Tissue harmonic imaging	Y	Y	Y	Y	Y
Contrast enhance capable	N	Y	Y	N	Y
Real-time elastography	Y	Y	Y	Y	Y
Strain ratio	N	Y	Y	N	Y
Strain histogram	N	N	Y	N	Y

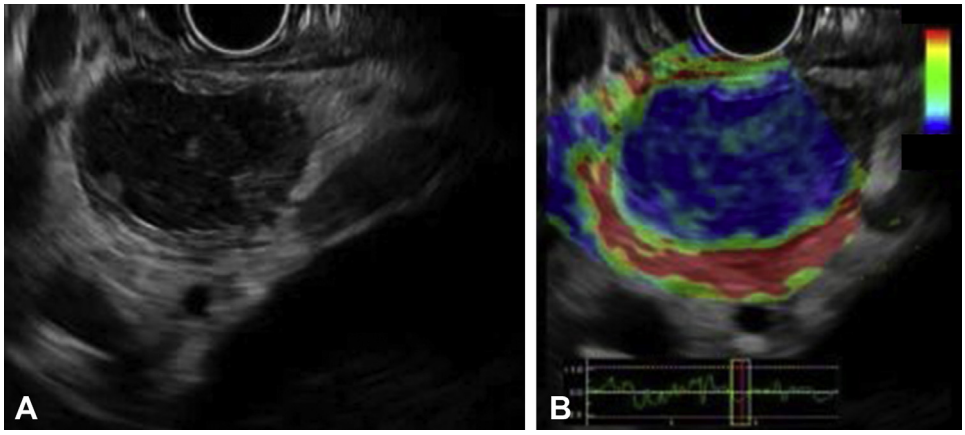

Figure 2. A large malignant perigastric node (**A**) that on sonoelastography appears to be stiff, hard, and blue (**B**). Note that the normal stomach wall between the transducer and the node is soft.

converted to a histogram that represents overall strain within a region of interest (Fig. 5). The integrated software then provides mean strain, standard deviation, and homogeneity of the strain based on the shape of the histogram. Combining both quantitative measures, investigators have developed a strain histogram ratio in which the mean strain from a histogram of the lesion is compared with the mean strain from a histogram of the reference area.[11-13]

Contrast-enhanced EUS

CE-EUS consists of an intravenous injection of contrast media during the EUS examination. It uses the altered vascular characteristics of malignancy compared with surrounding tissues to enhance visualization. Currently available contrast agents consist of microbubbles composed of an inert, relatively insoluble gas encapsulated by a protein, lipid, or polymer shell.[14,15] After intravenous administration, the microbubbles remain in the vascular space and enhance the visualization of blood vessels, from large vessels and heart chambers to the microcirculation within visceral organs. The contrast reaches maximum intensity in 20 to 30 seconds after injection but may last up to 5 to 10 minutes in the microcirculation.[16]

Contrast agents available in the United States include perflutren (Optison [GE Healthcare, Chicago, Ill, USA] and Definity [Lantheus Medical Imaging, Billerica, Mass, USA]) and sulfur hexafluoride (Lumason; Bracco Diagnostics, Inc, Monroe Township, NJ, USA). Optison and Definity are approved by the U.S. Food and Drug Administration (FDA) for use in patients with suboptimal echocardiograms to opacify the left ventricle and improve the delineation of the left ventricular endocardial borders. In addition to this indication, Lumason is also FDA approved in US of the liver for characterization of focal liver lesions and for the evaluation of vesicoureteral reflux in pediatric patients.

Color Doppler and power Doppler were the initial EUS modes used for CE-EUS but were hindered by poor detection of slowly flowing microcirculation and the presence of Doppler-related artifacts. Newer echoendoscopes with wider bandwidth transducers and processors with harmonic imaging software have improved resolution from areas of low blood flow when used with contrast media.[17] Tissue harmonic imaging uses nonlinear propagation of US waves to generate an image derived from the multiple harmonic waves generated by the transducer. This imaging mode is less susceptible to motion artifact than

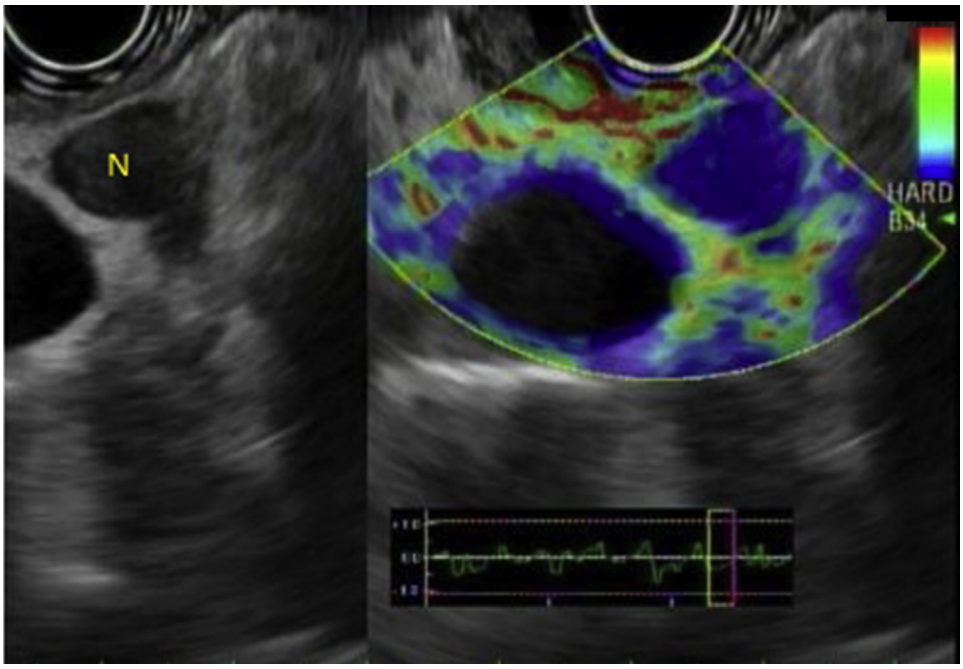

Figure 3. A paraesophageal lymph node seen by linear EUS that on split-screen elastography mode is seen as blue or hard and most likely malignant. EUS-FNA after elastography confirmed metastatic carcinoma.

standard Doppler modes and improves resolution of small blood vessels during CE-EUS.[18]

The intensity of enhancement during CE-EUS typically corresponds to lesion vascularity. Lesion vascular characteristics in both an early arterial phase and a later venous phase can be determined based on the timing of contrast administration during real-time EUS evaluation (Video 2, available online at www.giejournal.org). The arterial phase can be captured between 10 and 30 seconds from administration, with the venous phase between 30 and 120 seconds. EUS video loops were used to develop time-intensity curves to quantify the degree of lesion

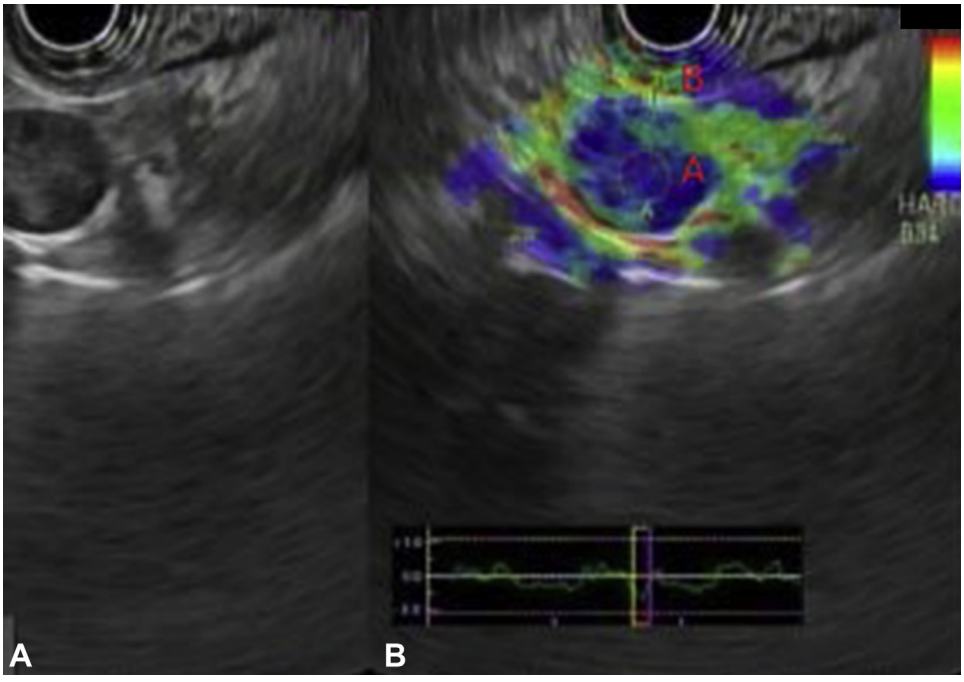

Figure 4. Quantitative sonoelastography of a mediastinal lymph node. A region of interest is selected within the area of interest (**A**) and compared with the stiffness of the normal GI wall between the transducer and the lesion (**B**) to calculate a strain ratio.

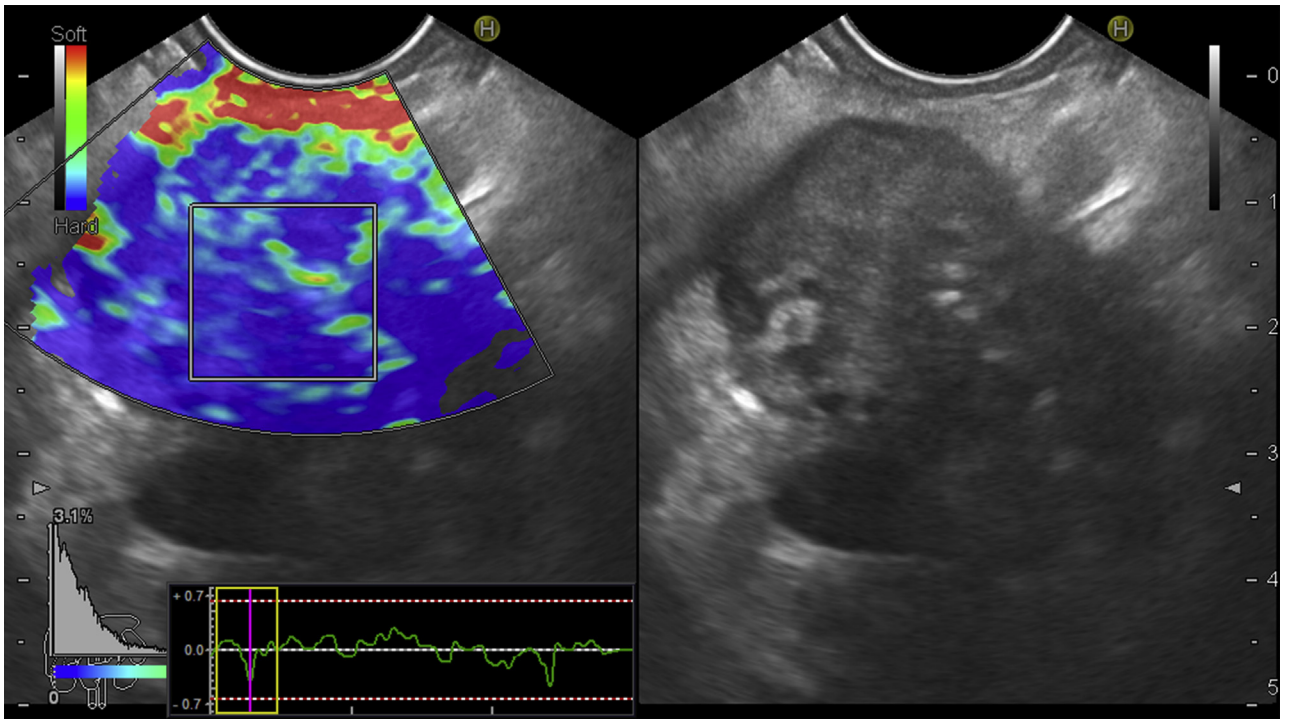

Figure 5. Strain histogram of a pancreatic adenocarcinoma. (Courtesy of Prof Adrian Saftoiu.)

enhancement as well as washout during the venous phase.[19]

OUTCOMES DATA

Elastography

Solid pancreatic masses. EUS-guided tissue acquisition (ie, FNA or fine-needle biopsy sampling) is a first-line diagnostic test for pancreatic mass lesions.[20-22] In a meta-analysis of 41 studies (4766 patients), the pooled sensitivity and specificity of EUS-FNA for the diagnosis of a solid pancreatic mass were 86.8% (95% confidence interval [CI], 85.5-87.9) and 95.8% (95% CI, 94.6-96.7), respectively.[22] Although the diagnostic accuracy of EUS-FNA for solid pancreatic lesions is high, factors such as chronic pancreatitis or infiltrative/desmoplastic lesions may reduce the accuracy.[23,24]

A meta-analysis of 17 studies (1537 patients, 1544 lesions) of EUS-EG in the evaluation of solid pancreatic masses reported the pooled performance characteristics of multiple EG measurement modalities.[25] The pooled sensitivity and specificity for qualitative methods were .97 (95% CI, .95-.99) and .67 (95% CI, .59-.74), respectively; the pooled sensitivity and specificity for strain histograms were .97 (95% CI, .95-.98) and .67(95% CI, .61-.73), respectively; and the pooled sensitivity and specificity for strain ratio were .98 (95% CI, .96-.99) and .62 (95% CI, .56-.68), respectively. Similarly, a prospective Italian study evaluated 102 solid pancreatic lesions (69 malignant, 33 benign) in 100 consecutive patients using EUS-EG.[26] In this series the parenchyma-to-lesion strain ratio and gastric wall-to-lesion strain ratio were significantly greater in malignant lesions than in benign lesions (24.5 vs 6.4 and 56.6 vs 15.3, respectively; $P < .001$ for both comparisons). When optimal cutoff values were used, EUS-EG had an 88.4% sensitivity and a 78.8% specificity for diagnosing malignancy. A multicenter study of 218 patients assessed the role of EUS-EG in evaluating small pancreatic lesions (<15 mm). In this study the determination by qualitative EG that a lesion appeared to be soft was associated with a 98% negative predictive value for ductal adenocarcinoma.[27] However, the specificity of EUS-EG for correctly predicting ductal adenocarcinoma in lesions with high stiffness was 67%. Of note, only 23% of the 218 patients in this study were found to have pancreatic cancer. Overall, these data indicate that EUS-EG is highly sensitive but poorly specific for diagnosing pancreatic cancer.

Lymph nodes. EUS-EG has also been investigated in the context of suspicious lymph nodes.[28-30] A meta-analysis of 7 studies (368 patients, 431 lymph nodes) with variable diagnostic standards (color pattern, strain ratio, histogram) and cutoff values summarized the performance of EUS-EG for the differentiation of benign from malignant lymph nodes. In this analysis the pooled sensitivity and specificity of EUS-EG were 88% (95% CI, .83-.92) and 85% (95% CI, .79-.89), respectively.[31] A subsequent study of lymph node characterization that used a histologic criterion standard reported a lower

sensitivity (55%-59%) and higher specificity (82%-85%) for EUS-EG as compared with traditional EUS criteria.[32] Although other single-center studies have reported more promising results for lymph node characterization using various scores derived from EUS-EG and B-mode imaging data, these approaches have not been replicated or externally validated.[33,34] The current performance characteristics of EUS-EG are inadequate to replace EUS-FNA of lymph nodes. However, EUS-EG has been proposed as an adjunct in the morphologic assessment and selection of specific lymph nodes for FNA or in the evaluation of peritumoral lymph nodes that cannot be sampled with FNA without traversing the primary tumor.[35]

Chronic pancreatitis. In a retrospective Japanese study of 96 patients with known or suspected chronic pancreatitis, pancreatic EUS-EG images were used to develop strain histograms, from which a mean elasticity value was calculated. There was a significant negative correlation between the mean elasticity value and the number of Rosemont criteria ($r_s = -.59$, $P < .001$).[36] The same authors retrospectively correlated preoperative EUS-EG parameters with the degree of histologic fibrosis (in the pancreatic parenchyma not involved by the tumor) in 58 patients undergoing surgical resection for pancreatic tumors. The mean elasticity value from the strain histogram was significantly correlated with the histologic grade of fibrosis.[37] Finally, a Spanish single-center prospective study evaluated 115 chronic pancreatitis patients using both EUS-EG and a ^{13}C-mixed triglyceride breath test to screen for pancreatic exocrine insufficiency. Patients with pancreatic exocrine insufficiency had a higher pancreatic-to-peripancreatic strain ratio (4.89; 95% CI, 4.36-5.41) than those with a normal breath test result (2.99; 95% CI, 2.82-3.16; $P < .001$). Similarly, the probability of pancreatic exocrine insufficiency was 87.0% (95% CI, 67.9-95.5) in patients with a pancreatic strain ratio greater than 4.5 compared with 16.3% (95% CI, 10.1-25.2) in those with a strain ratio less than 4.5 ($P < .001$).[38]

Chronic liver disease. Transabdominal US–based EG is now widely used to predict hepatic fibrosis noninvasively but may be less accurate in patients with ascites, thick subcutaneous fat, narrow intercostal spaces, and hepatic atrophy. Limited data exist on the accuracy of EUS-EG measurements for the evaluation of liver fibrosis. A prospective single-center study in the United States enrolled 50 patients with a clinical indication for upper EUS and recent abdominal imaging that indicated cirrhosis (n = 8), fatty liver (n = 16), or normal liver (n = 26).[39] During EUS, EG was performed and proprietary software was used to measure 9 elasticity-related variables. These data were then used to calculate a single liver fibrosis index. Patients with cirrhosis had significantly increased mean EUS-derived liver fibrosis index values compared with those with fatty liver (3.2 vs 1.7, $P < .001$) and normal values (3.2 vs .8, $P < .001$).

Contrast-enhanced EUS

Solid pancreatic masses. CE-EUS has been extensively studied as an adjunctive technique in the evaluation of solid pancreatic masses. In this setting, hypointensity during contrast administration is typically associated with adenocarcinoma, whereas neuroendocrine tumors are usually hyperintense or isointense relative to the normal parenchyma.[40,41] Chronic pancreatitis may appear as hyperintense or isointense.[42] Hyperintensity in the arterial phase has been reported in autoimmune pancreatitis.[43]

A meta-analysis of 12 studies (1129 patients) that described the performance of CE-EUS for the evaluation of solid pancreatic masses reported a pooled sensitivity of 94% and pooled specificity of 89% for pancreatic adenocarcinoma, using histology or ≥6 month clinical follow-up as a reference standard.[44] An updated meta-analysis using the same reference standard included 18 studies (1668 patients) and reported a pooled sensitivity of 92% and pooled specificity of 85%.[45] One study described the performance of the combination of CE-EUS after EUS-EG in 50 patients with a pancreatic mass and a negative FNA (ultimately determined to be pancreatic adenocarcinoma in 19 and pseudotumoral chronic pancreatitis in 31).[46] In the subset of 25 patients in whom EUS-EG indicated a lesion with high stiffness, subsequent CE-EUS was reported to have a specificity of 100% and accuracy of 93% for diagnosing malignancy.

A prospective multicenter European study reported the performance of CE-EUS in 167 patients with a solid pancreatic mass that was either pancreatic adenocarcinoma (n = 112) or chronic pancreatitis (n = 55), as determined by cytology or histology in 144 patients and during clinical follow-up in the remaining 23 patients.[47] The authors used proprietary software to construct and evaluate a multivariable time-intensity curve reflecting the characteristics of the wash-in and wash-out of contrast during a 60-second video clip. Further, the authors also created an artificial neural network to evaluate their data. The neural network could discriminate pancreatic cancer from chronic pancreatitis with a sensitivity of 94.6%, specificity of 94.4%, positive predictive value of 97.2%, and negative predictive value of 89.5%. A prospective pilot study of 26 patients with pancreaticobiliary malignancies who underwent subsequent surgical resection evaluated the additive benefit of CE-EUS to EUS (both in harmonic mode imaging) with regard to T-staging.[48] In this study a blinded reviewer evaluated video recordings of the examination. CE-EUS T-staging was concordant with histopathology in 24 of 26 cases (92.4%) as compared with 18 of 26 (69.2%) concordance for EUS without contrast ($P < .05$). A prospective tandem-controlled trial was performed comparing standard EUS with CE-EUS in patients with focal pancreatic lesions. In this study, CE-EUS increased the diagnostic yield compared with standard EUS with an

odds ratio of 7.8 (95% CI, 2.7-30.2). Time-intensity curves revealed distinct patterns for various pancreatic pathology and in a validation cohort were able to characterize 91% of lesions accurately.[49]

Pancreatic cysts. The utility of CE-EUS has also been reported in pancreatic cystic neoplasia, particularly with regard to the evaluation of mural nodules, which are known to harbor malignancy. Discriminating a true mural nodule from a mucin globule or clot during EUS B-mode imaging may be challenging, although distinguishing features have been described.[50] In a prospective, single-center Japanese study, 45 consecutive patients with intraductal papillary mucinous neoplasia diagnosed by CT underwent EUS examination.[51] In 17 patients in whom a suspected mural nodule was detected during B-mode imaging, CE-EUS was also performed to identify vascular flow in the suspected nodule. When compared with subsequent surgical pathology, CE-EUS correctly identified 12 of 12 mural nodules (sensitivity, 100%) but misidentified 1 of 5 mucin globules as a mural nodule (specificity, 80%). In a report that described 15 patients who underwent surgical resection for intraductal papillary mucinous neoplasia and suspected mural nodule, the accuracy of diagnosing mural nodules was 72% with standard EUS, 92% with CT, and 98% with CE-EUS.[52] In a Japanese, single-center, retrospective analysis of 70 patients with pancreatic cysts who underwent surgical resection, CE-EUS was more accurate than standard B-mode EUS imaging in the diagnosis of mural nodule-related malignancy (84 vs 64%, $P < .05$).[53]

Other applications. Other applications for CE-EUS include the evaluation of nonpancreatic lesions. In a retrospective, single-center study, both standard B-mode EUS and CE-EUS were used to evaluate 125 gallbladder lesions.[54] Video clips of the examination were then reviewed in a blinded manner by 5 experienced endosonographers who categorized the lesions as benign or malignant. The sensitivity and specificity of B-mode EUS were 82% and 100%, respectively, and the sensitivity and specificity of CE-EUS were 100% and 99%, respectively. The same group reported the use of CE-EUS in the evaluation of 157 subepithelial lesions in the upper GI tract, with surgical pathology serving as the reference standard. It was noted that 84.5% of GI stromal tumors demonstrated hyperintensity, whereas just 26.7% of benign lesions were hyperintense.[55] Thus, lesion hyperintensity during CE-EUS had a sensitivity of 84.5% and a specificity of 73.3% for the diagnosis of GI stromal tumor.

A recent systematic review of 6 studies evaluated the utility of CE-EUS when assessing submucosal lesions. The author noted a sensitivity of .86 (95% CI, .81-.90) and a specificity of .83 (95% CI, .34-.9).[56] Two studies have demonstrated a sensitivity >90% for the detection of malignant lymph nodes with CE-EUS using a histologic or cytologic reference standard. However, the specificity of CE-EUS in these studies was suboptimal, ranging from 60% to 80%.[57,58] A prospective study compared standard B-mode EUS with CE-EUS in 100 consecutive patients with lymphadenopathy. In this study, standard EUS criteria had a diagnostic sensitivity, specificity, and accuracy of 77%, 17%, and 59%, respectively, compared with 89%, 77%, and 85%, respectively, for CE-EUS (when using both quantitative and qualitative metrics).[59] A Korean study reported the use of CE-EUS in 30 patients with hepatic masses (28 malignant, 2 benign). During standard B-mode imaging, 22 of 30 masses (73%) could be visualized, whereas the addition of CE-EUS allowed clear visualization of 29 of 30 mass lesions (96.7%), facilitating subsequent EUS-FNA.[60]

Safety

Although there are no safety concerns related to EUS-EG, the performance of CE-EUS is associated with relevant safety issues. Administration of the available contrast agents during EUS represents an off-label use in the United States. In 2007, the FDA required a black box warning for all US contrast agents, stating that serious cardiopulmonary reactions, including fatalities, have occurred with their use, with most serious reactions occurring within 30 minutes of administration.[61] However, after review of extensive postmarketing data on cardiac patients, the FDA changed the labeling requirements in 2011 to reflect that serious adverse events were uncommon.[62] Overall adverse event rates are low (approximating .6%), with back pain and headache the most frequently reported adverse events.[63,64] Hypersensitivity to perfluoropropane is rare (.014%) but can be severe, including anaphylactoid or anaphylactic reactions.[41] A study of 5956 patients who received Definity reported 16 adverse events (.27%), with all events described as mild and transient.[62]

EASE OF USE

EUS-EG provides on-demand, real-time imaging, with both quantitative and qualitative analysis. Although the use of EUS-EG is not technically demanding and requires no additional formal training, the interpretation of the images and assignment of qualitative values is subject to interobserver variability, and undoubtedly there is a learning curve. Although quantitative measures should improve the reproducibility of EUS-EG findings, these metrics have not yet been fully standardized and validated.

Techniques for CE-EUS have been largely adapted from cardiac or abdominal SU protocols. Protocols for CE-EUS may be standardized, because the processor settings are the same as with transabdominal contrast-enhanced US. Two transabdominal contrast-enhanced US guidelines were published by the European Federation of Societies for Ultrasound in Medicine and Biology to discuss CE-EUS.[65] Experts from the European Federation of Societies for Ultrasound in Medicine and Biology, the World Federation for Ultrasound in Medicine and

TABLE 2. Currently available contrast agents with current cost*

Agent	Drug	Manufacturer	Cost/vial or unit
Optison	Perflutren protein-type A microspheres	GE Healthcare	$742/15 mL
Lumason	sulfur hexafluoride lipid-type A microspheres	Bracco Diagnostics	$766/5 units Supplied as a powder
Definity	Perflutren lipid microsphere	Lantheus Medical Imaging	$1119/8 mL

*Drug price information can be found at https://www.drugs.com/price-guide/.

Biology, and the Liver Imaging Reporting and Data Systems working group created a forum to standardize transabdominal contrast-enhanced US examinations, particularly with regard to the protocol for administration of contrast agents. The article generated by this working group is also applicable to the performance of CE-EUS.[66]

Briefly, a 20-gauge or larger peripheral intravenous catheter is preferred. Air filters should be avoided because they disrupt the microbubbles within the contrast agent. The contrast agent is given in a bolus of 1 to 2 mL/s. Immediately after injecting the contrast, a 5- to 10-mL bolus of saline solution is used to flush the intravenous line. Injections may be repeated depending on the indication.[18,66] The additional intraprocedural time required to perform CE-EUS has been reported to be minimal.[67,68]

FINANCIAL CONSIDERATIONS

EG packages are available from all 3 major U.S. vendors and may or may not require an additional software upgrade (Table 1). CE-EUS is optimally performed using a tissue harmonic imaging mode that is compatible with contrast-enhanced imaging. This is available in processors manufactured by Pentax and Olympus. Contrast agents available in the United States and their costs are detailed in Table 2.

At this time, no dedicated Current Procedural Terminology codes exist for EUS-EG or CE-EUS. Existing applicable base Current Procedural Terminology codes for EUS should be used (eg, 43259 or 43242) and in the case of CE-EUS, code 96374 (therapeutic, prophylactic, or diagnostic injection [specify substance or drug]; intravenous push, single or initial substance/drug) may also be reported. The Healthcare Common Procedural Coding System Level II codes Q9950 (injection, sulfur hexafluoride lipid microspheres, per mL) and Q9957 (injection, perflutren lipid microspheres, per mL) are also applicable when performing CE-EUS.

AREAS FOR FUTURE RESEARCH

Currently, the clinical roles for EUS-EG and CE-EUS are not well defined. Robust data indicate that neither technology has adequate specificity to serve as a stand-alone test for pancreatic malignancy. The proven safety and efficacy of EUS-guided tissue acquisition may limit the role for these techniques as primary diagnostic modalities. However, these modalities may improve the targeting of sampling to increase diagnostic yield, particularly for patients who have already undergone a negative FNA. They may also be useful in the evaluation of peritumoral lymph nodes and inflammatory pancreatic masses. However, standardization is lacking in outcome variables for different disease states with these technologies. The optimal training for these techniques is unknown, because they have primarily been evaluated in a limited number of expert centers.

EUS-EG appears to be feasible in the characterization of hepatic fibrosis, without the potential sampling error and risk associated with liver biopsy. However, the accuracy, reproducibility, and cost efficacy of this strategy remain to be determined. Early investigations have also suggested that EUS-EG strain ratios can correlate with the degree of physiologic pancreatic insufficiency. Further investigation is needed to determine the role for EUS-EG in the evaluation of chronic pancreatitis. The use of EUS-EG has also been reported for the evaluation of focal liver lesions, rectal cancer after radiotherapy, gastric subepithelial lesions, and various benign GI diseases.[69,70]

The use of CE-EUS may provide enhanced resolution to assess tumor vascularity in those patients receiving antiangiogenic chemotherapeutics.[71] Enhanced and more accurate imaging of splanchnic arterial or venous occlusive disease as well as varices in patients with portal hypertension has also been proposed.[72] Newer microbubbles that specifically target cancer cells on a molecular basis are also in development.[73] These approaches have the potential to increase the accuracy of diagnosis and determine the response to chemotherapy or radiotherapy. Finally, the use of chemotherapy-containing microbubbles, combined with EUS to facilitate cell permeability (sonoporation), may offer the potential for EUS-guided targeted therapy within a tumor.[74] The efficacy and safety of these target-specific agents await further study.

SUMMARY

EG and CE-EUS are technologies that may improve the real-time evaluation of intra- and extraluminal lesions as an adjunct to standard B-mode and Doppler imaging. They are not a replacement for EUS-guided tissue sampling but may provide additional diagnostic information

in specific clinical situations. The optimal use of these technologies continues to be a focus of ongoing clinical research.

DISCLOSURE

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CE-EUS, contrast-enhanced EUS; CI, confidence interval; EG, elastography; FDA, U.S. Food & Drug Administration.

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